IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Kitson , et al.	
Application No.: 09/780,060	
Filed: 2/9/2001	Group Art Unit: 1616
Title: Skin Treatment Compositions and Methods of Use	Examiner: M. Lamm
Attorney Docket No.: TDIG.P-001	

T. TUCK
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5/14/03
1691

BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the final rejection mailed 8/21/2002. Consideration of the application and reversal of the rejections are respectfully urged.

Real Party in Interest

The real parties in interest are the inventors. The Application is licensed to Dermex Therapeutics Inc. of Vancouver, Canada.

Related Appeals and Interferences

To Applicants' knowledge, there are no related appeals or interferences.

Status of Claims

Claims 1-40 have been submitted in this application. Claims 22-40 are withdrawn from consideration pursuant to a restriction requirement, but have not been cancelled since recombination of these claims would appear appropriate if the elected composition claims are

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I hereby certify that this paper and any attachments named herein are being deposited with the US Postal Service as first-class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on 28 April 2003.

Marina T Larson

Marina T. Larson, PTO Reg. No. 32,038

28 April 2003

Date of Signature

found to be allowable. Claims 10-13 are objected to as dependent on a rejected base claim. Claims 20 and 21 are cancelled in a concurrently filed amendment. Claims 1-9 and 14-19 are pending and are the subject of this appeal.

Status of Amendments

All prior amendments to the claims have been entered.

Summary of Invention

The instant invention provides a composition which, when topically applied to the skin of a mammal, reduces trans-epidermal water loss and provides an improved epidermal barrier. The composition comprises an aqueous dispersion of at least two lipids (Claim 1), preferably at least three lipids (Claim 2), in a non-crystalline phase lamellar array, preferably bilayer membranes in the form of liposomes. These lipids adopt a crystalline lamellar phase upon application to mammalian skin which resists washing with mild detergents and water.

Issues on Appeal

1. Are claims 1-3, 6-9 and 14-19 anticipated under 35 USC § 102 (e) by US Patent No. 5,916,578 of Kawada et al.?

2. Are claims 4 and 5 unpatentable under 35 USC § 103 in view of US Patent No. 5,916,578 of Kawada et al.?

Applicants submit that both of these questions should be answered the negative.

Grouping of Claims

Claims 1-3, 8-14 and 16-19 are argued as a first group, and stand or fall together.

Claim 4 is argued as a second group, which stands or falls separately. This claim is rejected under § 103, and presents issues different from the claims rejected as anticipated.

Claim 5 is argued as a third group, which stands or falls separately. This claim is rejected under § 103, and presents issues different from the claims rejected as anticipated and has greater differences from the disclosure of the Kawada reference than claim 4.

Claims 6, 7 and 15 are argued as a fourth group which stand or fall separately from other groups. In supporting the anticipation rejection of these claims, the Examiner relies on an external reference to demonstrate the supposed inherency of the limitations. This reliance is improper.

Argument

Claim 1 is not anticipated by the Kawada reference

The Examiner rejected claims 1-3, 6-9 and 14-21 under 35 USC § 102(e) as anticipated by US Patent No. 5,916,578 of Kawada et al. The characterized by the Examiner in the Office Action mailed January 2, 2002,

> Kawada et al. teach skin treatment compositions containing a liquid crystal phase containing a combination of a compound of a ceramide family, cholesterol and a fatty acid (e.g. palmitic acid) in the claim proportions. See col. 1, lines 5-10, col. 15, Compositions 26 and 27.

The Examiner also asserts that the limitation concerning the formation of a "crystalline lamellar phase" will be inherently met because the Kawada compositions contain the same ingredients.

While the Examiner is correct that the anticipation may be established where the limitations of the claim are inherently present in a prior composition, there are substantial limitations on the application of inherency. Specifically, inherency requires that any unstated elements be a necessary consequence of those which are stated. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Mehl/Biophile International Corp. v. Milgraum*, 52 USPQ2d 1303 (Fed. Cir. 1999). Here the Examiner has taken the position that because the reference recite some of the same component lipids, that it follows that the compositions must

have the recited properties. Applicants submit that this conclusion is both legally insufficient and scientifically incorrect.

The compositions of the Kawada patent are complex mixtures which happen to include some of the same components as the compositions of the invention. This, however, is not a sufficient basis to conclude that the compositions will inherently have the same properties. For example, omelets and cakes may share common ingredients (for example eggs and milk) but ordinary experience tells us they are not the same thing and do not have the same properties.

In the present case, compositions 26 and 27 of Kawada, on which the Examiner specifically relies, both contain cholestryl sodium sulfate, a material which is not included in any of Applicants' compositions. Second, compositions 26 and 27 contain oleylamino-octadecane-1,3 diol. This compound has a cis-double bond in the chain (oleyl is 9,10 unsaturated). Finally, compositions 26 and 27 are said to be hydrated with a very small amount of water (200 μl/20 g) and subjected to freeze thaw cycles. In contrast, the present invention is directed to aqueous formulations, and the lipid level in the aqueous buffer in Example 1 is 8 mg/ml. Persons skilled in the art know that water and the pH and salt concentration of that water are important determinants in the phase behavior of lipids. Here, the exemplary material in the present application has 125,000 times more water than the hydrated lipids of the reference. Despite all these differences between the Examples in the Kawada patent and the examples in the present application, the Examiner has naively assumed that because of some common ingredients the recited properties are inherent and must occur. No explanation has been provided by the Examiner as to why it would be reasonable to expect such different materials to act in the same way, and thus why it would be reasonable to expect that the Kawada compositions would necessarily crystallize.

Applicants have provided a Declaration under Rule 132, signed by the inventors of this case, which directly refutes the Examiner positions. A copy of this declaration is attached as Exh. A. In this declaration, the inventors state that their research with cholestryl sodium sulfate shows that it does not crystallize to the same extent as cholesterol. (¶ 2). Furthermore, with respect to oleylamino-octadecane-1,3 diol, the declaration (¶ 3) points out that this

compound has a cis-double bond in the chain (oleyl is 9,10 unsaturated), and that lipids with this stereochemistry are sterically unlikely to crystallize (See also page 5, ¶ 2 of the present application). As persons skilled in the art, the inventors also stated in their declaration (¶ 5) that "we do not think it would be reasonable to expect that the Kawada compositions would crystallize." Thus, the inventors have stated under oath the reasons why they do not believe that the Kawada compositions will crystallize. The Examiner has stated that the declaration is not commensurate with the scope of the claims because it does not say what happens when the composition is applied to skin. However, she has not provided any scientific reasoning or argument as to why the statement that the compositions will not crystallize (1) does not encompass the circumstance when the composition is applied to skin; and (2) why one might think application to skin would make the behavior of the composition different.

Finally, there is specific evidence in this case that the compositions of Kawada do not meet the limitations of the present claims concerning the formation of a crystalline phase. Kawada et al. actually provide data to show that their liquid crystals do ***not*** crystallize (col. 14, lines 18-19; column 13, lines 51-58). Thus, the compositions of Kawada are lamellar liquid crystals that do ***not*** crystallize, whereas the claimed invention is directed to non-crystalline phase lamellar lipid arrays (including but not limited to lamellar liquid crystals) that ***do*** undergo a phase transition to a crystalline lamellar phase.

Lest there be confusion based on the terms used in the art, a "liquid crystal," despite its name, is not a crystal. As pointed out on Page 4 of the present application, "a crystalline phase is defined as a physical state in which lipid membranes are organized on a lattice and have extremely reduced lateral and rotation mobility compared to the fluid arrangement of other mammalian cellular membranes." In other words, they are essentially a solid. In contrast, "non-crystalline phases" include liquid crystals, gels, and other recognized non-crystalline phases such as "liquid ordered" phases. As noted liquid crystals have some order, which is why the term "crystal" is used, but they are fluid. Thus, they are not crystalline as that term is used in the specification.

Applicants also attach as Exh. B a description of liquid crystals taken from the University of Wisconsin web site at http://scifun.chem.wisc.edu/chemweek/liqxtal/liqxtal.html. As shown in Fig. 1 of Exh. B, and described in the text, crystals have an ordered structure with the molecules in fixed positions. In contrast, Fig. 3 of Exh. B shows a lamellar liquid crystal, i.e., one in which the molecules are arranged in layers, or lamellae. This composition is still in a liquid state because the bonding forces are not equal in all directions, allowing both order and fluidity.

The Examiner has accepted the fact that a liquid crystal is not a crystal within the meaning of the present claims (Advisory Action mailed November 12, 2002), but has maintained the rejection based on inherency of crystallization, even though the reference itself says that crystallization does not occur, and notwithstanding Applicants' declaration. Applicants submit that this rejection is in error and that Kawada does not anticipate the present claims.

Since all of the rejections in this case are premised in the first instance on the interpretation of Kawada as inherently disclosing a composition within the scope of claim 1, the rejections claims 1-3, 6-9 and 14-19 should all be reversed. There are, however, additional flaws in the Examiner's position with respect to other claims which provide further grounds for reversal.

Claims 6, 7 and 15 are not anticipated by Kawada

Claims 6, 7 and 15 recite limitations setting forth the size and type of liposomes formed by the compositions of the invention. In this case, the Examiner states that "when the combination of lipids is mixed with aqueous phase by shaking the suspension, the liposomes formed are inherently multilamellar and have diameters from 100 to 3000 nm." (Office Action of 01/02/2002). In support of this position, the Examiner cites Col. 21, Ex. 7, and a secondary reference "Concise Encyclopedia Chemistry", Page 599. Kawada does not have an Example 7 in Col. 21. Kawada does not teach that liposomes form. Kawada does not teach that lipid particles of any particular type or size form. The secondary reference teaches the formation of multilamellar liposomes of the asserted size range by shaking a mixture of phosphatidyl choline

(egg lecithin), cholesterol and an acid component such as phosphatidic acid. These compositions are not even remotely similar to the compositions of Kawada, and provide no insight into what **necessarily** is true of the compositions of Kawada. Thus, the Examiner has failed to establish inherency for claims 6, 7 and 15.

Claim 4 is not obvious over Kawada

Claim 4 specifies that the composition comprises bovine brain ceramide, palmitic acid, and cholesterol in a ratio in the range of 1-5:1-5:1-5. The Examiner says that this composition is obvious over Kawada because Kawada says that the compositions of that invention achieve the same results as "a known natural ceramide extracted from bovine brain." In addition to the Examiner's improper rejection of claim 1 based on the flawed inherency argument, this rejection is further flawed because there is no articulated reason why a person skilled in the art would replace the ceramide in the Kawada composition with bovine brain ceramide. Basically, the art teaches that A+B+C+(other stuff) ≈ D. The Examiner argues from this that it would be obvious to make D+B+C+(other stuff). No reasons for this argument are offered. Thus, the Examiner has failed to present a *prima facie* case of obviousness.

Claim 5 is not obvious over Kawada

Claim 5 specifies that the composition comprises ceramide 2, palmitic acid, and cholesterol in a ratio in the range of 1-5:1-5:1-5. The Examiner says that this composition is obvious over Kawada because Kawada says that the compositions of that invention achieve the same results as "a known natural ceramide extracted from bovine brain." In addition to the Examiner's improper rejection of claim 1 based on the flawed inherency argument, this rejection is further flawed because there is no articulated reason why a person skilled in the art would replace the ceramide in the Kawada composition with ceramide 2. Basically, the art teaches that A+B+C+(other stuff) ≈ D. The Examiner argues from this that it would be obvious to make X+B+C+(other stuff), where X is not mentioned in the reference. No reasons for this argument are offered. Thus, the Examiner has failed to present a *prima facie* case of obviousness.

Conclusion

In view of the foregoing, Applicants submit that claims 1-3, 6-9 and 14-21 are allowable over the cited Kawada et al. patent. Reversal of the rejection is respectfully urged.

Respectfully submitted,

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APPENDIX
CLAIMS ON APPEAL

1. A skin barrier replacement composition comprising an aqueous formulation of at least two lipids in a non-crystalline phase lamellar array which adopt a crystalline lamellar phase upon application to mammalian skin.

2. The composition of claim 1, comprising at least three lipids.

3. The composition of claim 2, wherein the at least three lipids comprise a ceramide, a saturated fatty acid and cholesterol.

4. The composition of claim 3, comprising bovine brain ceramide as the ceramide, palmitic acid as the saturated fatty acid and cholesterol in ratios by mol of from 1-5:1-5:1-5, respectively.

5. The composition of claim 3, comprising ceramide 2 as the ceramide, palmitic acid as the saturated fatty acid and cholesterol in ratios by mol of from 1-5:1-5:1-5, respectively.

6. The composition of claim 2, wherein said aqueous formulation of lipids consists of multilamellar vesicle or large unilamellar vesicle liposomes or a mixture thereof.

7. The composition of claim 6, wherein said liposomes have a median diameter of 15 to 1500 nm.

8. The composition of claim 2, wherein said crystalline lamellar phase forms after penetration into the stratum corneum of the skin.

9. The composition of claim 2, wherein said non-crystalline phase is a liquid crystal

14. The composition of claim 2, wherein the aqueous formulation contains no organic solvent or alcohol.

15. The composition of claim 2, wherein the aqueous formulation is sufficiently polar to support multilamellar vesicle formation

16. The composition of claim 2, wherein the composition contains no squalene.

17. The composition of claim 2, wherein the lipid mixture contains no phospholipid or glucosylceramide

18. The composition of claim 2, wherein the lipid mixture contains no unsaturated fatty acid.

19. The composition of claim 2, wherein the lipid mixture contains no surfactant.